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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/066,320	01/31/2002	Jonathan S. Stamler	1818.1030-003	1921

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EXAMINER

GUPTA, ANISH

ART UNIT PAPER NUMBER

1654

DATE MAILED: 07/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

<p align="center">Office Action Summary</p>	Application No. 10/066,320	Applicant(s) STAMLER ET AL.	
	Examiner Anish Gupta	Art Unit 1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 4-28-05.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 4-6 is/are pending in the application.
- 4a) Of the above claim(s) 1-3 and 7-29 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 4-6 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

1. The amendment filed 4-28-05 is acknowledged. Claims 4-6 were amended. Claims 1-29 are pending in this application.

Election/Restrictions

2. This application contains claims 1-3 and 7-29 drawn to an invention nonelected with traverse in Paper No: 9-17-04. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

3. All rejections made in the previous office action and not maintained herein, are hereby withdrawn.

Maintained Rejections

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

- (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
- (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is

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determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

New Grounds For Rejections

4. Claims 4 remains rejected under 35 U.S.C. 102(b) as being anticipated by Jia et al (Nature).

The claims are drawn to a method of producing S-nitrosohemoglobin by adding NO to a composition comprising oxyhemoglobin.

Applicants argue that Jia reports the addition of free NO to oxyhemoglobin produces methemoglobin rather than S-nitrosohemoglobin. "Prior to the instant case, it was universally believed that free NO combined with hemoglobin to produce methemoglobin, which destroyed NO bioactivity." Jia does not teach or suggest that free NO can be added to oxyhemoglobin to produce S-nitrosohemoglobin. Jia obtains a different product and thus cannot anticipate the claimed invention.

Applicants arguments, filed 2-25-05, have been fully considered but have not been found persuasive.

Claim 4 reads: "A method of producing a composition comprising S-nitrosohemoglobin, said method comprises adding free NO to a composition comprising oxyhemoglobin." The active method step in the claim is the "adding free NO to a composition comprising oxyhemoglobin."

Note that Jia, as Applicants acknowledge in their arguments, teaches the addition of NO to oxyhemoglobin (see page 222). Thus, the reference discloses the identical active method step as the claimed invention. Since the reference discloses the same method steps as the claimed invention, the same product would necessarily be achieved. Applicants have not shows that the claimed method step differs from the prior at method step.

The rejection is maintained.

Claim Rejections - 35 USC § 112

5. Claims 5-6 are rejected under 35 U.S.C. 102(e) as being anticipated by Yonetani et al.

The claims are drawn to a method of producing S-nitrosohemoglobin by adding NO to a composition comprising oxyhemoglobin.

The reference teaches that Nitric oxide in the blood is well maintained at a steady-state level of the order of micromolar by the dynamic balance between the continuous supply of NO by endothelial NO synthases and other sources and the rapid scavenging of NO by oxy hemoglobin (oxyHb) in the erythrocytes. Nitric oxide in the blood rapidly diffuses into erythrocytes and reacts with oxyHb (see col. 16, lines 1-8). Thus, the reference discloses the identical active method step as the claimed invention. Since the reference discloses the same method steps as the claimed invention, the same product would necessarily be achieved.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 4-6 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the conditions necessary to achieve S-nitrosylhemoglobin. The prior art states nitric oxide, when introduced with oxyhemoglobin, results in the formation of methemoglobin. "Methemoglobin formation occurred instantaneously on addition of NO." (see page 222 of Jia). Nitric oxide in the blood rapidly diffuses into erythrocytes and reacts with oxyHb

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and forms metHb and NO.sub.2.sup.- /NO.sub.3.sup.- (see Ynoetani et al. col. 16, lines 1-8).

Thus, a single method step of adding free NO to oxyhemoglobin is not sufficient since this step leads to methemoglobin

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 4-6 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

(1) The nature of the invention:

The invention is drawn to Nitric Oxide and its interaction with various forms of :

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hemoglobin.

(2) The state of the prior art

The prior art states nitric oxide, when introduced with oxyhemoglobin, results in the formation of methemoglobin. "Methaemoglobin formation occurred instantaneously on addition of NO." (see page 222 of Jia). Yonetani et al. States Free NO in the plasma constantly diffuses into the erythrocyte and immediately reacts with Hb, which acts as a NO scavenger. It has been generally assumed that free NO in the blood is scavenged by rapid reaction with oxyHb to produce such bio-inactive products as metHb and nitrate under physiological conditions (see paragraph bridging col. 1-2). Nitric oxide in the blood rapidly diffuses into erythrocytes and reacts with oxyHb to form metHb and NO₂⁻ /NO₃⁻ (see col. 16, lines 5-10).

(3) The relative skill of those in the art

The relative skill of the those in the art is high.

(4) The predictability or unpredictability of the art

Given the state of the art, it is relatively predictable to conclude that when nitric oxide with combined with oxyhemoglobin will result in the formation of methemoglobin. This is also true when nitric oxide is subjected to erythrocytes.

(5) The breadth of the claims

Claim 4 is drawn to "[a] method of producing a composition comprising S-nitrosohemoglobin, said method comprises adding free NO to a composition comprising

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oxyhemoglobin.” Claim 5 and 6 recite the a method producing intraerythrocytic NO by adding free NO to a composition comprising oxygenated erythrocytes.

(6) The amount of direction or guidance presented and (7) The presence or absence of working examples

The specification is silent as to the conditions necessary to achieve the claimed product of S-nitrosylHb. It is not always the case that when NO is added to oxyhemoglobin that S-nitrosylHb is obtained. For example, Example 3 of the specification shows the effects of free NO to oxyhemoglobin. The examples utilize a specific buffer that either 100 mM phosphate, 10mM phosphate and 10mM+.05% borate (see page 46). The results indicate that when 100 mM phosphate was used, formation of metHb was observed. Using 10mM phosphage shows the formation of iron nitrosyl Hb and some metHb. Using 10mM phosphate + borate resulted in predominantly iron nitrosylHb. Thus when phosphate is present in a concentration of 10mM the desired S-nitrosylHb is not obtained, rather Fe-nitrosylHb is obtained.

The prior art also reflects the concept that NO added to oxyhemoglobin does not always lead to the formation of S-nitrohemoglobin. Jia, as Applicant asserted on page 4 of the response dated 2-25-05, reports that addition of free NO to oxyhemoglobin produces methemoglobin rather than S-nitrosohemoglobin (see page 222, figure 1B). Yonetani et al. teaches that Nitric oxide in the blood is well maintained at a steady-state level of the order of micromolar by the dynamic balance between the continuous supply of NO by endothelial NO syntheses and other sources and the rapid scavenging of NO by oxy hemoglobin (oxyHb) in the erythrocytes. Nitric oxide in the blood rapidly diffuses into erythrocytes and reacts with oxyHb and forms metHb and NO.sub.2.sup.- /NO.sub.3.sup.- (see col. 16, lines 1-8).

Given these teachings, one cannot readily conclude that addition of free NO to

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oxyhemoglobin or oxygenated erythrocytes will result in the formation of S-nitrosohemoglobin, as the claims currently recite. Rather specific conditions are necessary to make desired end product. The instant specification does not describe the desired conditions to achieve S-nitrosohemoglobin. It is not as simple as adding free NO to oxyhemoglobin as indicated by Yonetani and Jia et al. Accordingly, one would be burdened with undue experimentation in determining the appropriate conditions for obtaining S-nitrosylhemoglobin rather than obtaining methemoglobin or iron-nitrosylhemoglobin.

(8) the quantity of experimentation necessary

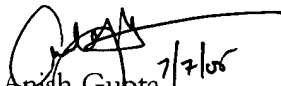
For the reasons set forth above, one would be burdened with undue experimentation in determining the appropriate conditions for obtaining S-nitrosylhemoglobin rather than obtaining methemoglobin or iron-nitrosylhemoglobin.

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

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9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anish Gupta whose telephone number is (571)272-0965. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell, can normally be reached on (571) 272-0974. The fax phone number of this group is (571)-273-8300.


Anish Gupta 7/7/06
Patent Examiner